REMARKS

The only issue outstanding in the Office Action of December 8, 2010, is the rejection of all pending claims under 35 USC §103. Reconsideration of this rejection in view of the following discussion, is respectfully requested.

Claims 1, 3-5 and 9-16 remain rejected under 35 USC §103 over Reynolds (US 3,808,332) taken with Mitra (US 5,955,105) and Remington's Pharmaceutical Sciences. Reconsideration of this rejection is again requested.

Reynolds discloses a pharmaceutical composition comprising a carrier and the reaction product of tertiary phosphine with thyroxine and 3, 5, 3'-L-triiodothyronine. The present and prior Office Actions have established that Reynolds fails to teach gelatin in the combination. The secondary references also fail to suggest the use of gelatin "as a binder", as recited in the present claims. Mitra is cited for the proposition that "proper selection" of a binder and filler, and disintegrant, lubricant, etc. is necessary to produce a stable formulation for levothyroxine in solid dosage form. However, with regard to specific binders disclosed therein, Mitra only generically discloses that "suitable compatible" binders, disintegrant, lubricants, etc. should be used. See col. 3, lines 30-32. Indeed, such would be apparent to one of ordinary skill in the art. In fact, Mitra contains a very specific teaching as to how to improve stability of a levothyroxine preparation. Mitra teaches that stability is increased by the use of an inorganic salt, a carbohydrate having molecular weight greater than 500 or glycine, see col. 2, lines 61-67. Mitra teaches that lactose, glucose and sucrose are incompatible with their formulation, see col. 3, lines 30-31. Thus, Mitra does not suggest particular binders, much less gelatin.

It is further important to realize that Mitra does not teach avoidance of lactose, glucose, sucrose etc. as *binders* with thryoxine, but refers to them only as fillers. Note that Mitra describes these "excipients" as "bulker or diluent", thus clearly a filler, not a binder. With respect to the difference between fillers and binders, it is well known to those of ordinary skill in the formulation art that the function of auxiliaries in a pharmaceutical formulation depend on the composition as well as the process of manufacture. If, for example, a concentrated sugar solution

(i.e. a syrup) is mixed with other ingredients and subsequently dried, it will form a crust. Within such a crust sugar has a binding function so that it can be called, within the limits of such a formulation, a binder. However, if the sugar is used in a dry form and if it is compressed to a tablet, such sugar does not execute a binding activity but acts as a filler, i.e., the sugar does little or nothing to hold the tablet together. The same applies to starch, which together with water can form a starch paste and, if mixed with other auxiliaries and dried, may have a binding function. If starch is used within a formulation as a dry powder, however, the starch has no binding activity and its function is again that of a filler. By contrast, where gelatin is used as an aqueous solution leading to formulation, it functions as a binder, holding the tablet together.

The formulation of the present examples contain a sugar, starch, gelatin, levothryxoine sodium as the active ingredient and magnesium stearate as a lubricant. If there were no difference between binders and fillers, as apparently they are used interchangeably in the office action, then the tablet of the present invention would besides the active ingredient and the lubricant contain only binders. This would not make any sense. In fact, one of ordinary skill in the art would see that in the formulation of the present invention maize starch and lactose monohydrate act as fillers, whereas gelatin has the function of a binder. This is because only gelatin is dissolved and used as a solution (wherein levothyroxine is suspended).

Thus, Mitra does not eliminate lactose, glucose, sucrose etc. as binders, but as bulkers or fillers. Mitra teaches different binders than these materials, including microcrystalline cellulose, maltodextrin, starch and hyroxpropyl cellulose, see col. 4, lines 12-14. Gelatin is not mentioned. As a result, one of ordinary skill in the art is not left with a choice between only starch and gelatin where levothryoxine is concerned, even considering the well known disclosure of Remington. In fact, a large number of binders are known in the pharmaceutical field, as demonstrated by the previously submitted excerpt from the pharmaceutical dictionary Hunnius Pharmazeutisches Worterbuch. "The Hunnius" is the standard dictionary in the pharmaceutical field, it is present in nearly every German-language pharmaceutical library, pharmacy and pharmaceutical laboratory. As clearly set forth herein under "Bindemittel" (which means binders): *"Als B. warden verwendet: Zucker, Starken, Gelatine, Cellulosederivate, Gummi*

arabicum, Tragant, PEGs, PVP u.v.a" meaning *As binders are used: sugars, starches, gelatin, cellulose derivatives,gummi arabicum, traganth, polyethylene glycols, polyvinyl pyrrolidone* and many others. A multitude of different binders exist, from which the binder has to be selected.

Applicants have previously maintained that the two declarations of record further establish the non-obviousness, and thus patentability, of the present claims. In the first Declaration, comparison is made between a formulation containing gelatin, and one containing the polymer HPMC, (hydroxypropylmethylcellulose). The declaration shows that, unexpectedly, where gelatin is substituted for HPMC as a binder, active agent content over time is significantly greater for compositions formulated with gelatin then the active agent content maintained for those formulated with HPMC. One of ordinary skill in the art would not expect such a beneficial and significant stability effect for gelatin, as nowhere in the cited references is any advantage taught for gelatin; gelatin is simply one of many possible fillers or binders. In the second Declaration it is shown that a formulation according to the invention, which contains a small amount (2.50 mg) of gelatin as binder has a better stability than the same formulation containing 3.50 mg HPMC, which is the most frequently used binder. The improvement of stability further increases with the amount of gelatin in a dose-dependent way.

However, the present Office Action, while indicating that the Declarations are persuasive "in part", in that they indicate better stability of a formulation containing a small amount of gelatin, argues that they are not commensurate in scope of the claims. Applicants respectfully disagree with this analysis. At page 4 of the Office Action, it is argued that the Declarations show an improvement for 2.50 mg of gelatin versus 3.50 mg of HPMC. The Declaration of February 2008 further shows that considerable improvement is also established for 10 mg of gelatin, in formulation C. Thus, it is submitted that the improvement is found independent of the amount of gelatin. It is noted that the Office Action argues that claims limited to "formulation A" would be favorably considered. However, formulation A is a prior art formulation. Accordingly, Applicants have amended the amount of gelatin present in the claims to that disclosed in the present examples in the specification. It is submitted that this amount, 5 mg, would clearly maintain the unexpected results shown in the February 2008 Declaration, and as a

result is non-obvious over the cited references. Withdrawal of all rejections is accordingly respectfully requested.

The claims of the application are submitted to be in condition for allowance. However, if the Examiner has any questions or comments, she is cordially invited to telephone the undersigned at the number below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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